REMARKS

Claim 1 has been amended to set it forth as a method of treatment and to specify method steps.

Claims 2-9 have been amended to be consistent with amended claim 1.

Claims 13-26 have been canceled.

New claims 27-29 have been added. Claim 27 specifies the nanomolar range as being between 1 and 100. Support for this claim can be found at page 8, lines 18-20. Claims 28 and 29 specify that a long term therapeutic effect is achieved with a single administration and that this lasts for up to ten days. Support for these claims can be found at page 9, lines 14-15.

It is submitted that these amendments do not constitute new matter, and their entry is requested.

Rejection Under 35 USC § 101

Claims 1-9 and 13-23 were rejected under 35 USC § 101, for being in improper form. Claims 1-9 have been amended to set forth a proper method and to include proper method steps. Claims 13-24 have been canceled.

In view of the above amendment and remarks, it is submit that the present claimed subject matter is in a proper format. Withdrawal of this rejection is requested..

Rejection Under 35 USC § 112, second paragraph

Claims1-9 and 13-23 were rejected under 35 USC § 101, for being in improper form. Claims 1-9 have been amended to set forth a proper method and to include proper method steps. Claims 13-24 have been canceled.

In view of the above amendments and remarks, it is submitted that the present claimed subject matter is definite. Withdrawal of this rejection is requested.

Rejection Under 35 USC § 102(b)

Claims 1-6, 8 and 9 were rejected under 35 USC § 102(b) as being anticipated by Sherman et al. (US 6,096,711). The Examiner contends that Sherman et al. teaches a method for treating ischemic conditions (ischemic cerebral infarction, ischemic acute renal failure, intestinal ischemia and ischemic heart disease) by administering a proteosome inhibitor to a patient. The proteosome inhibitor may be MG132. Finally, the Examiner contends that Sherman et al. teaches that the administration of a proteosome inhibitor during atherosclerotic disease of epicardial coronary arteries or myocardial infarction can minimize damage and provide a therapeutic window for surgical intervention. Applicants submit that Sherman et al. does not anticipate the presently claimed subject matter.

First, Applicants note that Claim 1 has been amended to specify that the administration of the therapeutic effect of at least one proteosome inhibitor is sufficient to produce an enhancement in the expression of eNOS and that this amount is in the nanomolar range. Applicants submit that Sherman et al. does not teach the claimed method.

Specifically, Sherman et al. teaches that contacting an aged cell with a proteosome inhibitor, e.g., MG1323, results in an induction of Hsp72 expression in the cell while not committing the cell to apoptotic death. The Hsp72 expression is induced to a level sufficient to suppress stress-activated kinase activity, such as JNK and/or p38 activity. On the basis of this disclosure, Sherman et al. teaches "transiently" administering a proteosome inhibitor to an aged individual for treating pathologies associated with apoptosis and inflammation. The amount of proteosome inhibitor administered is sufficient for inducing Hsp72 production. Sherman et al. discloses using 1.5 mM or 10mM MG132. See, column 12, lines 10-15 and column 11, lines 44-46, respectively. "Transient" exposure is defined at column 4, lines 40-53 as a sufficient concentration for a sufficient length of time to induce Hsp72 production to levels sufficient for suppression of stress-activated kinase activity. Sherman et al. does not disclose the use of a proteosome inhibitor to enhance the expression of eNOS, which enhancement can be long term, i.e., up to ten days, based on a single

administered dose that is in the nanomolar range. Since Sherman et al. does not disclose these elements of the claimed invention, Sherman et al. cannot anticipate the amended claims.

In view of the above amendments and remarks, it is submitted that the present claimed subject matter is not anticipated by Sherman et al. Withdrawal of this rejection is requested.

Rejection Under 35 USC § 103(a)

Claims 1-6, 8 and 9, 13-19 and 21-23 were rejected under 35 USC § 103(a) as being obvious over Sherman et al. (US 6,096,711). The Examiner states that Sherman et al. does not teach the use of nanomolar concentrations of MG132. However, The Examiner contends that it would have been obvious to optimize concentration through routine experimentation. Applicants submit that Sherman et al. does not render the presently claimed subject matter obvious.

First, Applicants note that Claim 1 has been amended to specify that the administration of the therapeutic effect of at least one proteosome inhibitor is sufficient to produce an enhancement in the expression of eNOS and that this amount is in the nanomolar range. Claims 13-19 and 21-23 have been canceled. Applicants submit that Sherman et al. does not suggest the claimed method.

Specifically, as described above, Sherman et al. does not disclose or suggest the use of a proteosome inhibitor to enhance the expression of eNOS, which enhancement can be long term, i.e., up to ten days, based on a single administered dose that is in the nanomolar range. In the absence of any such suggestion in Sherman et al., Applicants submit that Sherman et al. cannot render the presently claimed invention obvious.

Furthermore, Applicants submit that although there may be some desire to optimize the concentration of a given drug as contended by the Examiner, there is nothing in Sherman et al. that would suggest administering the drug for the disclosed purposes in a nanomolar range. In fact, based on the prior art disclosed at page 4 of the present application, Applicants note that it appears that the prior would not suggest using a dosage of a proteosome inhibitor at the nanomolar range. There is no suggestion or reasonable prediction in the prior art that a nanomolar dose of at least one

proteosome inhibitor would be effective for enhancing the expression of eNOS. There is also no suggestion or reasonable prediction in the prior art that a single administration of such a dose could have a long term enchancement of the expression of eNOS, especially in view of Sherman et al.'s disclosure of a transient effect. Thus, Applicants submit that Sherman et al. does not render the presently claimed invention obvious.

In view of the above amendments and remarks, it is submitted that the present claimed subject matter is not rendered obvious by Sherman et al. Withdrawal of this rejection is requested.

Conclusions

In view of the above amendments and remarks, it is believed that the claims satisfy the requirements of the patent statutes and are patentable over the prior art. Reconsideration of the instant application and early notice of allowance are requested. The Examiner is invited to telephone the undersigned if it is deemed to expedite allowance of the application.

Respectfully submitted,
ROTHWELL, FIGG, ERNST & MANBECK, p.c.

By /Jeffrey L. Ihnen/

Jeffrey L. Ihnen
Registration No. 28,957
Attorney for Applicants
1425 K Street, N.W., Suite 800
Washington, D.C. 20005
Telephone No.: (202) 783-6040
Facsimile No.: (202) 783-6031

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